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#14
DB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Boyce et al.

EXAMINER: Prebilic, P.

SERIAL NO.: 09/543,268

GROUP ART UNIT: 3738

FILED: April 5, 2000

DATED: January 14, 2003

FOR: OSTEOIMPLANT AND METHOD FOR ITS MANUFACTURE

DOCKET: 285-79 CON

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF TODD M. BOYCE UNDER 37 C.F.R. § 1.131

Sir:

I, Todd M. Boyce, Ph.D., declare and say as follows:

1. I am a Senior Scientist with Osteotech, Inc., the assignee of record of the subject patent application, and a named inventor therein.

2. In the Office Action mailed October 23, 2002, the Examiner has rejected Claims 1-7, 9-21, 23-43, 45-61, 63-80 and 82-134 of the subject patent application under 35 U.S.C. § 102(e) as unpatentable over Boyce et al. U.S. Patent No. 5,899,939 ("Boyce et al.") which issued on May 4, 1999 on original application Serial No. 09/009,997 filed January 21, 1998.

3. I am also the first named inventor on the Boyce et al. patent.

4. The subject application was filed on April 5, 2000 as a continuation of U.S. patent application Serial No. 09/020,205 filed February 6, 1998 which issued as U.S. Patent No. 6,123,731 on September 26, 2000.

5. I make this Declaration under 37 C.F.R. § 1.131 in order to present a showing of facts evidencing the making of the claimed invention in this country prior to the January 21, 1998 filing date of the aforesaid Boyce et al. application.

6. All of the acts described hereinafter took place in the United States.

7. Annexed Exhibit A of which I am the author is a true copy of a memo and accompanying drawings, redacted to remove references to dates and non-relevant subject matter, that was prepared prior to January 21, 1998.

8. Examples 2, 3, 4 and 5 of Exhibit A describe embodiments of the invention of amended Claim 1 herein. These examples conclusively show that prior to the January 21, 1998 filing date of the application underlying the grant of Boyce et al. U.S. Patent No. 5,899,939, the invention herein had been completed in this country.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: Jan. 14, , 2003

Todd M. Boyce

Exhibit A

OSTEOTECH

Memorandum

DATE:

TO: Peter Dilworth, Dilworth & Barrese

FROM: Todd Boyce

RE: 285-79: Osteoimplant and method for its manufacture

(VIA FAX; Originals to follow by post)

Attached are the background information materials that I promised, regarding the second application, 285-79. In this FAX transmittal are included:

- A document describing materials for claim 5, background information on cross-linking of collagen, the use of glycerol to maintain hydration, and five example descriptions.
- Hand-drawn pictures to accompany the five examples.

In the copy that I send to you by mail, I'll also include the articles by Lewandrowski, Jurgensen, and an article that one of my co-workers found on fibrin glues used with hydroxyapatite to make implants for bone replacement.

I've tried to include information that I thought you might need. Please fell free to call me (732-544-6235) if I have missed important points, or if I have been unclear in any of this. Nelson and I look forward to moving ahead with this application, and to working with you further as it develops.

97_1105a

285-79: List of materials for Claim 5:
The group including glycerol, any tanning agent, substances imparting radioopacity, metallic meshes, hydrophilic components, antibiotic and/or antiviral agents, activated protein-based binders, lysine-rich proteins, allogenic or xenogenic serum albumin, allogenic or xenogenic fibrin, thrombin or other blood or serum elements, allogenic or xenogenic collagen, collagen glues, fibrin glues, polymethyl methacrylate, cyanoacrylate, autologous bone cells or stem cells, hydroxyapatite or other calcium-phosphate-based minerals, calcium sulfate, bioglass, cancellous bone, any of the family of bone morphogenic proteins, transforming growth factor beta, Insulin-like growth factor, calcium chloride, glucose or other sugars.

In addition to what we currently have, Claim 1 could also generalize to bone elements which might be either cortical or cancellous, or combined corticocancellous in structure.

The list of bones for claim 11 is given in my correspondence to you on application 285-79.

The list of osteoinductive materials for claim 18 is also given in my correspondence to you re: application 285-79. Osteogenic osteoinductive and osteoconductive materials for claim 24 are also given there.

285-79: Collagen cross-linking

Collagen is a naturally-occurring structural biomaterial, and is a part of connective tissues, including bone, in all vertebrate species. The native collagen molecule is a glycine-rich chain of amino acids, arranged in a triple helix. It is known that collagen-containing tissues may be preserved by cross-linking the collagen molecules together by any of a number of means, including chemical reaction, the application of radiant energy, dehydrothermal treatment, or enzymatic treatment. In each case, exposed functional groups of the collagen amino acids react to form stable intra- and inter-molecular bonds. These bonds act to stabilize the tissue against breakdown, and impart additional mechanical strength. These approaches are used in the preparation of biomaterials, in fixation of tissues for histological processing, in tanning of leathers and furs, in embalming, and in other manufacturing

Bone is made of collagen, hydroxapatite mineral, and other non-collagenous proteins. The present invention removes the mineral in bone by treating the bone with acid

solutions, detergents, or chelating agents, and then placing surface-demineralized particlesin contact with each other. The assembled construct is then treated with a cross-linking agent or process to cross-link the collagen molecules, providing bonding or adhesion between particles. Furthermore, since acid demineralization is a diffusion-limited reaction, with an advancing reaction front (2), bone-derived particles may be demineralized at the surface, exposing the collagen there, while leaving the inner core of the particle fully mineralized. The depth of demineralization is a function of the strength of the acid solution, the shape of the particle, and the treatment time. (2). Suitable compounds for demineralizing bone include hydrochloric acid, hydrofluoric acid, acetic acid, sulfuric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, hydrosulfuric acid, nitric acid, nitrous acid, perchloric acid, chloric acid, chlorous acid, hypochlorous acid, hypochlorous acid, acetic acid, sulfurous acid, carbonic acid, boric acid, ethylene diamine tetraacetic acid (EDTA). The most useful of these are solutions of hydrochloric acid, acetic acid, and EDTA.

Chemical cross-linking agents usually contain bifunctional or multifunctional reactive groups, which react with functional groups on the amino acids, such as the ε-amine functional group of the lysine or hydroxylysine, or the carboxyl functional groups of aspartic and glutamic acids. By reacting with multiple functional groups of different collagen molecules, the reacting chemical creates a reinforcing cross-bridge. Chemicals which act as collagen cross-linkers include: mono- and dialdehyes, including glutaraldehyde and formaldehyde; Polyepoxy compounds such as glycerol polyglycidal ethers, polyethylene glycol diglycidal ethers and other polyepoxy and diepoxy glycidal ethers; Tanning agents including polyvalent metallic oxides such as such as titanium dioxide, chromium dioxide, aluminum dioxide, zirconium salt, as well as organic tannins and other phenolic oxides derived from plants; esterification of carboxyl groups followed by reaction with hydrazide to form activated acyl azide functionalities in the collagen; dicyclohexyl carbodiimide and its derivatives as well as other heterobifunctional cross-linking agents; hexamethylene diisocyanate. Sugars, including glucose, will also cross-link collagen; this is a patholological process which can occur in living diabetic patients. Chemical cross-linking of the exposed collagen will involve exposing the assembled bone-derived pieces to the chemical agent, either by placing it in a solution of the chemical agent, or by exposing it to the vapors of the chemical agent at an appropriate pH and temperature, and for times ranging from minutes to days, depending upon the level of cross-linking desired, and the activity of the chemical agent. The chemical agent is then washed to remove all leachable traces of the chemical

Glutaraldehyde cross-linked biomaterials have a tendency to over-calcify in the body. Calcification-controlling agents which might be used with aldehyde cross-linking agents include: dimethyl sulfoxide (DMSO), Surfactants, diphosphonates, aminooleic acid, and metallic ions, primarily ions of iron and aluminum.

Physicochemical and physical methods for cross-linking tissues include: Dye-mediated photo-oxidation, irradiation by UV light or microwaves, drying and/or heating, dehydrothermal methods (in which water is slowly removed while the tissue is in a vacuum).

Enzymatic treatment is another way to introduce cross-links between the collagen molecules. Treatment by enzymes such as tissue transglutaminase can catalyze reactions between the gamma carboxylic acid group of amino acids to the amino group of lysine in the collagen molecules. This approach has been used previously to bond cartilage (1), however our application here is a novel use which provides bonding between partially or fully demineralized bone pieces, and imparts substantial mechanical strength to the bonding interface.

285-79: Use of glycerol to maintain hydration and prevent separation of bone elements

Following the creation of an osteoimplant, and for the purpose of storage prior to implantation, the osteoimplant may require free water to be removed, via freeze-drying, or other drying steps. We have found that in this process, residual strains in the mineral-containing bone elements making up the osteoimplant may cause warping of layered constructs, which in turn may produce separation between cross-link bonded components. The addition of an aqueous glycerol-containing solution or other additive helps to maintain hydration of the osteoimplant, and reduces or eliminates this warping effect.

285-79 Examples:

Example 1 (Pilot 28): Slices of compact bone, each approximately 1.5 - 2 mm thick were placed into excess 0.6 N HCl solution for 1.5 hours with constant stirring. The pieces were washed in water for 5 minutes, and soaked for 1.5 hours in BupH phosphate buffered saline (Pierce, Catalog #28372). The slices were stacked into layers, and were clamped together. The clamped construct was then placed into a solution of 10% neutral buffered formalin for 48 hours to cross-link the exposed collagen surfaces. After cross-linking, the clamp was removed, and the construct was placed in a water bath to rinse in running water for several hours. The construct was cut to shape on a band saw, and then placed in an excess aqueous solution of glycerol. After seven hours, the excess glycerol solution was removed, and the osteoimplant was freeze-dried.

Example 2 (Pilot 11F): Elongate bone fibers were milled from cortical bone, and were fully demineralized in excess 0.6N HCl solution. These fibers were washed with water, and soaked in an aqueous solution of glycerol. Fully mineralized fibers were added, and the solution was stirred and left for 12 hours at room temperature. The solution containing the soaked mineralized and demineralized fibers were poured through a micron sieve to recover the fibers. The fibers were then pressure-treated to 10,000-50,000 psi in a press for 15 minutes, and were then heated for 2 to 12 hours at 37-55 degrees C. The resulting osteoimplant pellet was freeze dried, and placed in polyethylene glycol diglycidal ether for 12 hours at room temperature.

Example 3 (pilot 14): Human cortical bone slices, approximately 1 mm thick by 7mm wide by 5cm long, were treated for 10 minutes in 0.6 N HCl to expose surface collagens. Human cancellous bone cubes, 1cm x 1 cm x 1cm, were treated to expose surface

collagens at the outer borders of the cubes. All slices and cancellous bone cubes were washed in water. The pieces were assembled together with cortical slices bordering the cancellous blocks, and clamped into place. The construct was then placed into a solution of 10% neutral buffered formalin for 3 hours to crosslink the exposed collagens. The resulting osteoimplant was then washed in water, and cut to size on a band saw.

Example 4 (Pilot 21): Human bone segments, approximately 1mm thick were surface demineralized for 15 minutes in 0.6N HCl, then washed in running water. Tissue transglutaminase was reconstituted to give a 1mg/ml solution. For each layer of the construct, the surface was blotted dry, then 40µl/cm^2 area of the tissue transglutaminase was applied to one side of a demineralized bone slice, and an equivalent volume of 0.1M $CaCl_2$ solution was applied to the mating surface of the next bone slice. This was repeated sequentially. The resulting construct was clamped and placed into a humidity chamber for approximately 30 minutes, then washed in water.

Example 5: Cortical bone slices, approximately 2mm thick, were surface demineralized in 0.6N HCl solution for 1 hour with constant stirring. Bone slices were coated with dry, demineralized bone powder having a particle size of 300 microns or less, and assembled into layers. The construct was clamped into place, and placed into a solution of 10% neutral buffered formalin for 12 hours to permit collagen cross-linking. The resulting osteoimplant was washed in water to remove excess chemicals.

References

1. Jürgensen K, Aeschlimann D, Cavin V, Genge M, Hunziker EB: A new biological glue for cartilage-cartilage interfaces: Tissue transglutaminase. *J Bone Joint Surg [Am]* 79-A:185-193, 1997
2. Lewandrowski K-U, Venugopalan V, Tomford WW, Schomacker KT, Mankin HJ, Deutsch TF: Kinetics of cortical bone demineralization: Controlled demineralization -- a new method for modifying cortical bone allografts. *J Biomed Mater Res* 31:365-372, 1996

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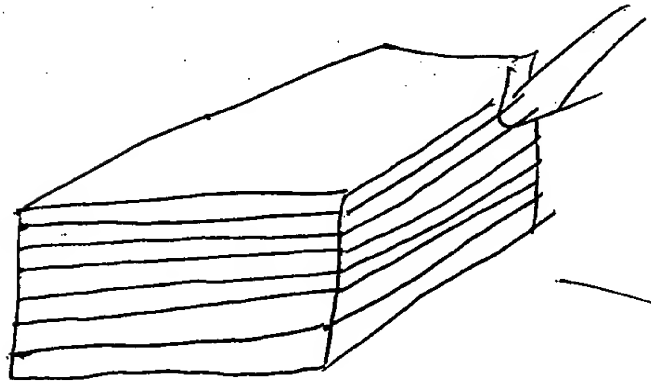
285-79 EXAMPLE 1 :

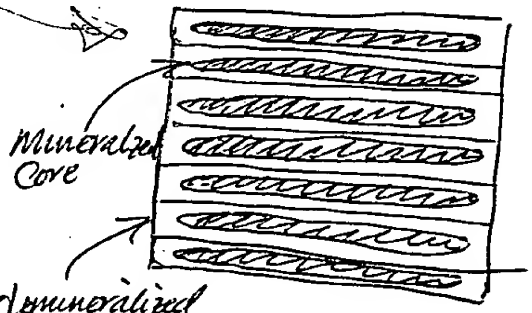
Cortical Bone Strips

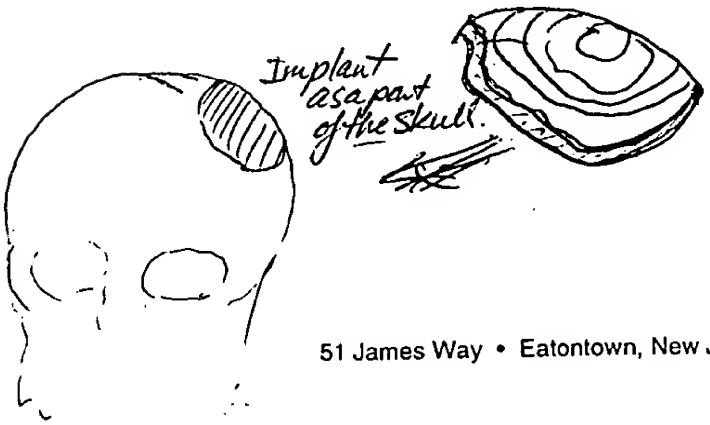
Surface Demineralize in Acid.

Clamp together Cross-link.



Appearance through Cross-section:





Machined to shape - (Parietal Bone - portion)

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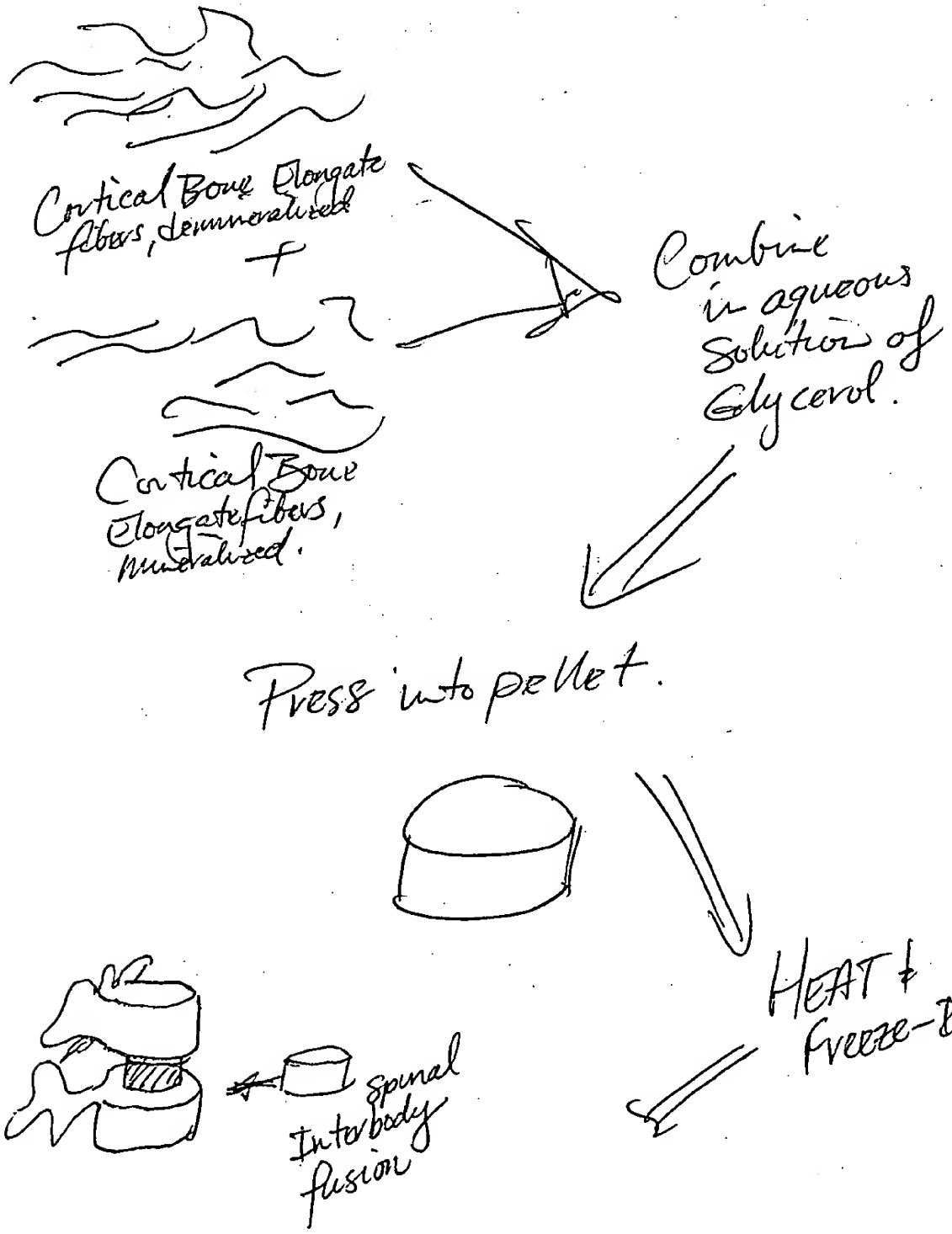
285-79 EXAMPLE 2:



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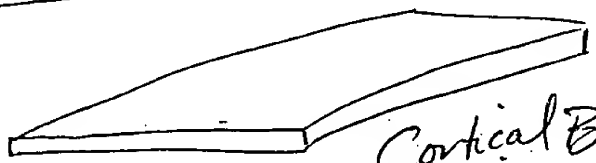
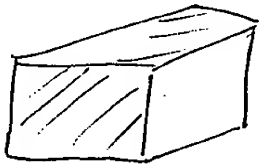
285-79 EXAMPLE 3.



Cortical Bone Strip

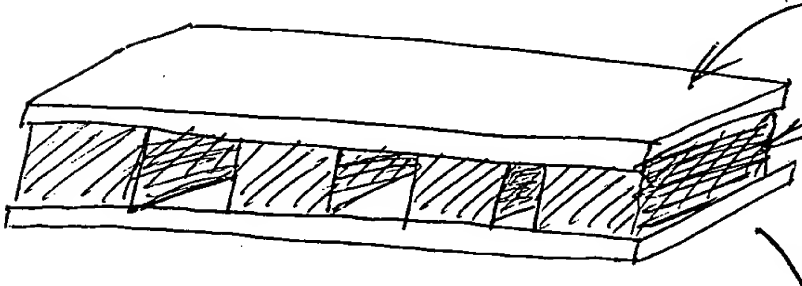
+



Cancellous Bone Block

Surface Demineralize

Clamp in place
Cross-link



Cortical

Cancellous

Cut & Shape.

used as a spinal onlay graft for ~~fusion~~ posterolateral intertransverse process fusion.

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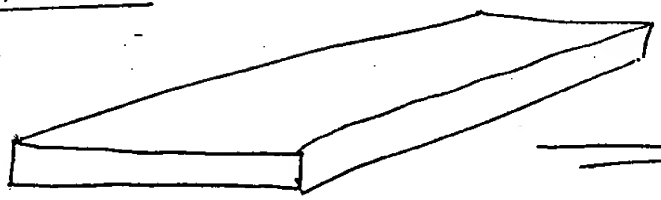
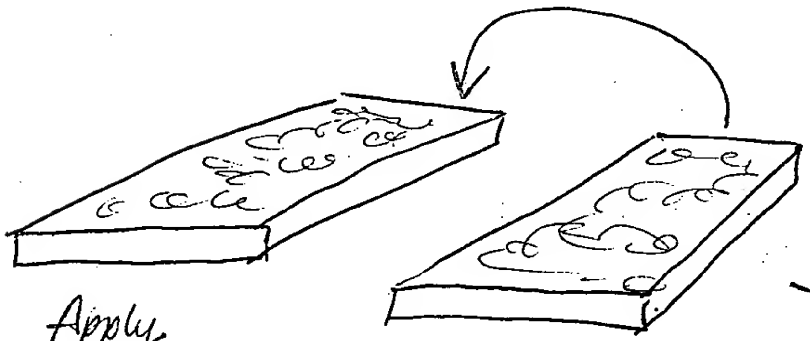
EXAMPLE 4:



Cortical Bone Slices

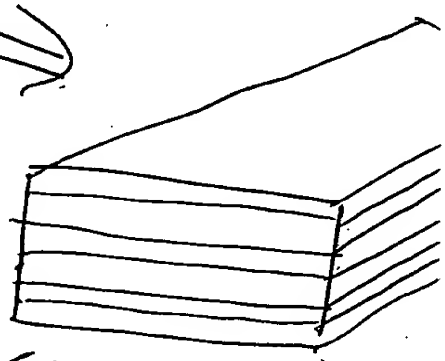
Surface Demineralize with Acid, Wash.



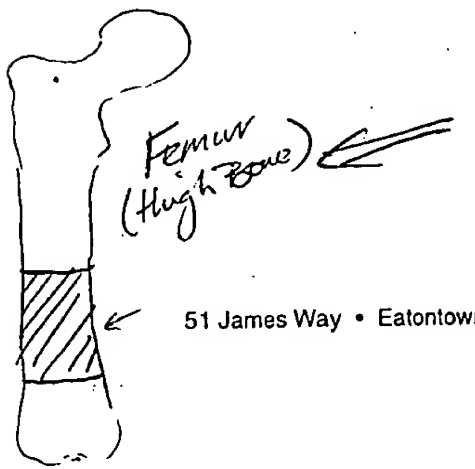
Apply Tissue Transglutaminase

Apply $CaCl_2$ Solution.

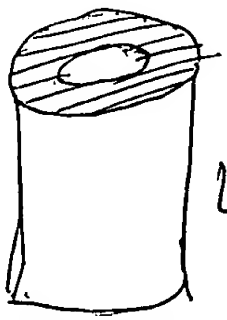
Then assemble with treated surfaces touching



Machine to shape.



Femur (Thigh Bone)



Long bone segment replacement.

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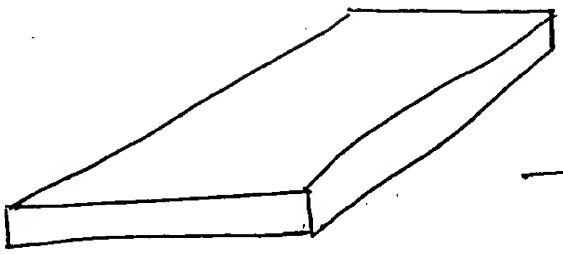
285-79

EXAMPLE 5:



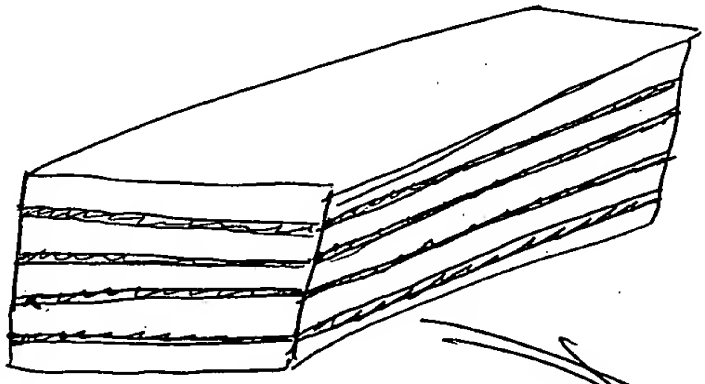
Cortical Bone Slice

→ Surface Demineralize with Acid

+

Cortical Bone Powder.

→ Fully Demineralize with Acid.



Layer with powder betw. slices. Clamp and Cross

Machine to shape

Proximal Tibia Shape.

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Medical Device & Diagnostic Industry Magazine
MDDI Article Index

An *MD&DI* September 1999 Column

SPECIAL SECTION

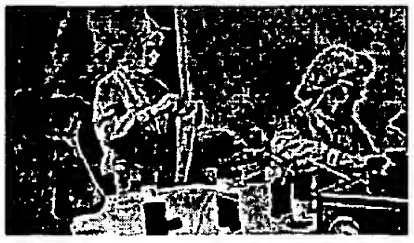
ADHESIVES TECHNOLOGY

Advances in Cyanoacrylate Technology for Device Assembly

The latest generation of adhesive products offer manufacturers a range of properties to meet their application requirements.

Patrick J. Courtney and Christopher Verosky

Cyanoacrylates are solvent-free, one-part adhesives that cure rapidly when pressed into a thin film between two surfaces. Their ease of use and availability in USP Class VI–qualified formulations have made them attractive to manufacturers of a wide variety of medical devices. Unfortunately, earlier generations of cyanoacrylates had significant performance limitations, such as poor thermal resistance and peel strength. Consequently, many medical device manufacturers were unable to take advantage of the processing advantages that these adhesives offer. Subsequent developments in cyanoacrylate technology have greatly expanded the performance of these adhesives and led to products that offer the ease of use of a cyanoacrylate coupled with the performance of a true structural adhesive.



Cyanoacrlate adhesives provide benefits that make them advantageous for medical device manufacturing.

The intent of this article is to provide an overview of cyanoacrylate technology, with an emphasis on the technical developments that have led to these performance improvements. This overview comprises a brief explanation of cyanoacrylate chemistry, a summary of the common types of cyanoacrylates and the key developments in cyanoacrylate technology that have led to performance enhancements for these products, and descriptions of the critical adhesive process and performance properties of interest to end-users. Finally, the introduction of rubber-toughened, surface-insensitive, thermally resistant cyanoacrylates—which offer advantages over earlier generations of toughened products—is highlighted.

CYANOACRYLATE ADHESIVE CHEMISTRY

Cyanoacrylates are one-part, room-temperature-curable adhesives that are available in a wide range of viscosities. When confined in a thin film between two surfaces or sprayed with a chemical activator, cyanoacrylates cure rapidly to form rigid thermoplastics with excellent adhesion to most substrates. Cyanoacrylates typically fixture within 1 minute and achieve full bond strength in 24 hours. These types of adhesives are familiar to the general public under brand names such as Super Glue, Quick-Tite, and Krazy Glue.

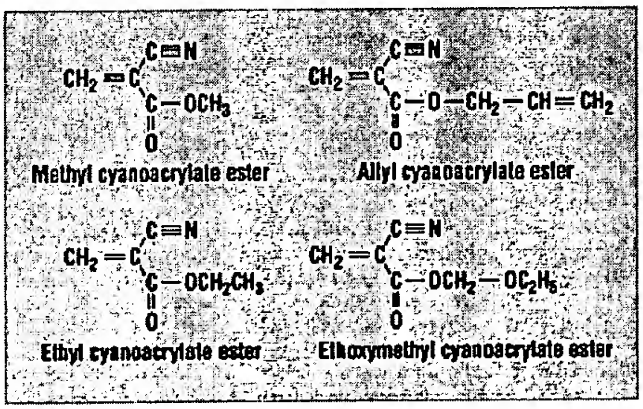
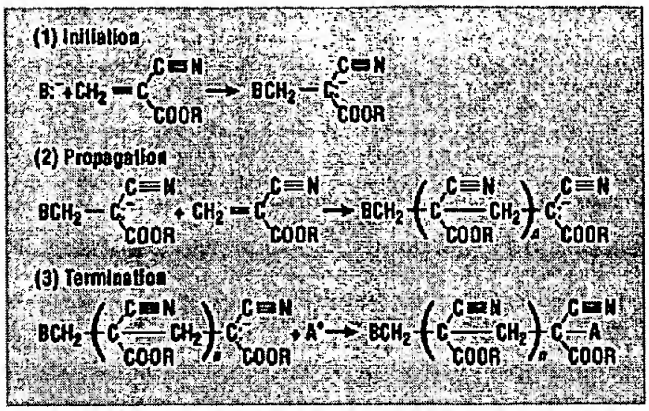


Figure 1. Common cyanoacylate monomers.

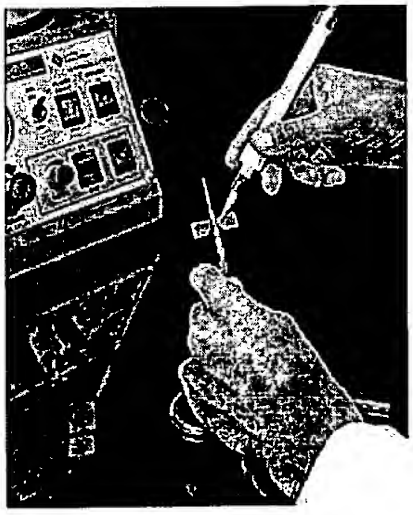
Cyanoacrylate adhesives are cyanoacrylate esters, of which methyl and ethyl cyanoacrylates are the most commonly used in adhesive formulation (Figure 1). Cyanoacrylates undergo anionic polymerization in the presence of a weak base such as water, and are stabilized through the addition of a weak acid. When the adhesive contacts a surface, trace amounts of water or other species present on the surface neutralize the acidic stabilizer in the adhesive, resulting in the rapid polymerization of the cyanoacrylate (Figure 2).



TYPES OF CYANOACRYLATES

The relative benefits and limitations of various cyanoacrylates make them appropriate for different applications.

Methyl Cyanoacrylates. Methyl cyanoacrylates are based on the methyl cyanoacrylate monomer (Figure 1). Formulations based on this monomer were the first commercially available cyanoacrylate products. This monomer has the lowest molecular weight of any cyanoacrylate monomer, and consequently leads to the most rigid polymer matrix. While generally superior to ethyl cyanoacrylates for metal-bonding applications, they do not offer the durability of rubber-toughened products on metallic substrates.



The latest generation of cyanoacrylate offers the ease of use of a one-part formulation and the performance of a structural adhesive.

Ethyl Cyanoacrylates. Ethyl cyanoacrylates are based on the ethyl cyanoacrylate monomer, the most commonly used monomer in cyanoacrylate adhesives (Figure 1). In general, ethyl cyanoacrylates are considered to offer superior performance on plastics and elastomeric substrates compared with methyl cyanoacrylates.

Low-Odor, Low-Bloom Cyanoacrylates. Cyanoacrylates have a sharp, irritating odor that can be unpleasant if proper ventilation is not used. The volatility of cyanoacrylate monomer can also lead to the formation of a white haze, known as blooming, around the cyanoacrylate bond line. Blooming occurs when cyanoacrylate monomer volatizes and settles around the bond line in the form of minute crystals of polycyanoacrylate resin. Although this is purely an aesthetic problem and does not affect the performance of the adhesive in the bonded joint, it is unacceptable in many manufacturing processes.

Blooming can be minimized through adequate ventilation, removal of excess adhesive, and rapid curing via proper adhesive selection and/or the use of an accelerator. Another solution involves the use of adhesives based on cyanoacrylate alkoxy ester monomers, which because of their higher molecular weight are less volatile than standard ethyl and methyl cyanoacrylates (Figure 1). Consequently, they do not have as strong an odor and are less likely to cause blooming.

Surface-Insensitive Cyanoacrylates. Cyanoacrylates are stabilized through the addition of trace amounts of acidic species: it is the neutralization of the acidic stabilizer by trace amounts of moisture or other species that leads to the polymerization of the cyanoacrylate adhesive. On acidic surfaces, such as wood or dichromated metals, or in low-humidity environments, the neutralization of the acidic stabilizer may be hindered, leading to long fixture times. To address this limitation, surface-insensitive cyanoacrylates were developed by adding agents such as silacrowns, crown ethers, and calixarenes to ethyl cyanoacrylates. By minimizing the effect of surface acidity and dryness, these products generally offer the most rapid fixture times of all cyanoacrylates.

Toughened Cyanoacrylates. Given their rigidity, cyanoacrylates generally have low peel and impact strength. Not surprisingly, a great deal of effort has gone into addressing this limitation through the development of toughened cyanoacrylates. These efforts are described later in the article, in the subsection devoted to peel and impact strength.

Thermally Resistant Cyanoacrylates. As a result of their thermoplastic nature, cyanoacrylates typically offer very

limited high-temperature performance. Generally, at 188°F and above they soften considerably, and the bond strength drops precipitously. Early attempts to alter this characteristic involved the development of cyanoacrylates based on allyl cyanoacrylate esters (Figure 1). These materials could be cross-linked through the allyl group, resulting in a thermoset polymer matrix. Unfortunately, such systems had to be fixtured during the heat-cure step, as the cyanoacrylate would soften well below the temperatures required to initiate cross-linking. Subsequent developments in thermally resistant cyanoacrylate technology have involved the use of unique additives to produce products that provide long-term bond strength at temperatures as high as 250°F for thousands of hours without a heat-cure step. These developments are explored more fully in the subsection on thermal resistance.

Thermally Resistant, Rubber-Toughened, Surface-Insensitive Cyanoacrylates. The latest developments in cyanoacrylate technology combine the performance advantages of earlier generations of thermally resistant, rubber-toughened cyanoacrylates with additional features. These are described in detail following the review of the benefits and limitations of current cyanoacrylate technologies.

ACCELERATORS AND PRIMERS

The capabilities of cyanoacrylate adhesives can be expanded through the use of specialty accelerators and primers.

Cyanoacrylate Accelerators. Cyanoacrylate accelerators are made up of an active species dispersed in a solvent such as acetone or isopropyl alcohol. The active species is generally a base that is capable of initiating the cure of the cyanoacrylate adhesive. Accelerators can be applied to the substrates being bonded prior to adhesive application in order to minimize fixture time. Generally, the accelerator is applied to one surface while the adhesive is applied to the mating surface, which prevents curing of the adhesive by the accelerator before the parts can be mated. Accelerators can also be sprayed over cyanoacrylates to cure fillets of adhesive or unconfined drops. This technique is widely used for wire tacking on printed circuit board assemblies.

Polyolefin Primers. Low-surface-energy plastics such as polyolefins, fluoropolymers, and acetal resins are typically difficult to bond with any adhesive. Special primers have been developed that allow improved bond strengths to be achieved

with cyanoacrylates on these types of materials (Figure 3). These primers are made up of an active species—typically a tertiary amine—dispersed in solvent. The primer is applied to the substrate, which is ready for bonding once the solvent has evaporated.

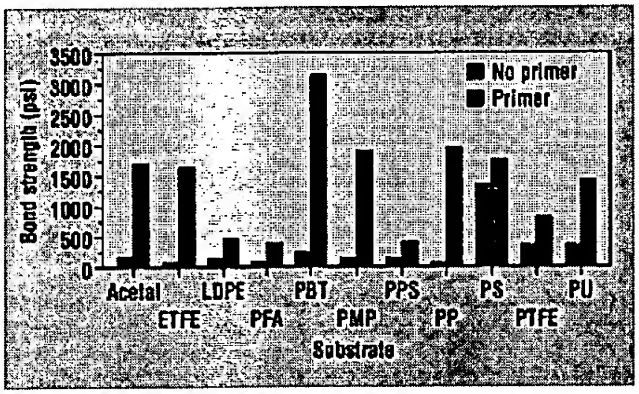


Figure 3. Effect of polyolefin primers on bond strength of surface-insensitive ethyl cyanoacrylate to plastics. All assemblies tested in accordance with ASTM D 4501 (block shear method). (ETFE = ethylene tetrafluoroethylene copolymer, LDPE = low-density polyethylene, PFA = polyperfluoroalkoxyethylene, PBT = polybutylene terephthalate, PMP = polymethylpentene, PPS = polyphenylene sulfide, PP = polypropylene, PS = polystyrene, PTFE = polytetrafluoroethylene, PU = polyurethane.)

Investigations into the specific method by which the primers enhance bond strength have identified two likely mechanisms. One theory is that the accelerating effect of the amine on the curing reaction enhances bond strength. It is thought that the heat released during the rapid exothermic reaction of the accelerated polymerization raises the temperature of the polymer layers in intimate contact with the adhesive and leads to improved diffusion of the cyanoacrylate polymer chains into the polymer substrate. While this mechanism may account for some of the effectiveness of the primers, it does not explain why primary and secondary amines—which also act as accelerators—are not very effective polyolefin primers.

The second phenomenon, which is thought to play a more critical role in bond-strength development, is diffusion of the alkyl chains of the tertiary amine into the polymer surface. This leaves the nitrogen with the free-electron pair at the surface to act as an initiation site for the cyanoacrylate polymerization. In this way, the tertiary amine is believed to promote bond strength by acting as an "anchoring site" for

the cyan-oacrylate. This explanation would be consistent with the observation that the effectiveness of polyolefin primers increases as the crystallinity of the plastic they are used on decreases, since the more amorphous substrates would facilitate diffusion of the alkyl chains.[1]

KEY PROPERTIES OF UNCURED (LIQUID) CYANOACRYLATES

In the adhesive's uncured state, the most important characteristic of interest to the end-user is the viscosity of the cyanoacrylate. Cyanoacrylates are available in viscosities ranging from water-thin liquids to thixotropic gels. The driving force behind the development of products with such a wide range of viscosities has been the need to meet end-users' varying application requirements. For example, the low-viscosity products, also known as wicking-grade adhesives, can be applied to assemblies after the components have been fitted together. The cyanoacrylate will then rapidly fill the bond area through capillary action. In some cases, the low viscosity of wicking-grade products is a disadvantage because it makes the placement of the cyanoacrylate difficult to control. Given the propensity of the adhesive to fill gaps and rapidly polymerize, the ability to control its placement is critical.

To address this need, higher-viscosity products and thixotropic gels were developed through the addition of thickeners such as polymethylmethacrylate resin and silica. While the wicking-grade-viscosity products will tend to run out of any gap larger than 0.001–0.002 in., the higher-viscosity products can be used on much larger gaps. The gels can even be applied to inverted or vertical surfaces and will not drip or run. It is still best to keep joint gaps no larger than 0.010 in., even though these products can be used in still-larger gaps without flowing. The limiting factor in joint-gap design for the higher-viscosity products is the ability of the adhesive to cure through the entire gap. One must remember that the cyanoacrylate curing process is surface initiated, and consequently it is difficult to achieve complete cure when a large volume of the adhesive is not in close proximity to a surface.

Most types of cyanoacrylate are commercially available in the entire range of viscosities, with the exception of the rubber-toughened cyanoacrylates. The addition of the rubber to the

formulation raises the viscosity such that wicking grades of the rubber-toughened cyanoacrylates cannot be produced.

KEY PROPERTIES OF CYANOACRYLATES DURING CURING (LIQUID TO SOLID)

Cyanoacrylates are known for their rapid fixture and cure speed. Figure 4 shows typical fixture speeds of three types of cyanoacrylates on a variety of substrates. When reviewing such data, it is important to understand what is meant by fixture speed. Adhesive manufacturers will cite the time required to develop a certain shear strength as the fixture speed of the adhesive. In the testing done to generate the data shown in Figure 4, the fixture time was defined as the time required for the adhesive to achieve a shear strength of 14.5 psi when tested in accordance with ASTM D 1002.

While such testing is valuable for making comparisons between adhesives, it should be noted that the actual fixture time for an adhesively bonded joint of an assembly on the manufacturing floor may differ significantly from the value found on a product data sheet. In a manufacturing process, the fixture time of an adhesively bonded joint is the time required for the joint to develop sufficient strength for the assembly to proceed to the next step in the manufacturing process. For example, if the joint has a large bond area and bears very little load, the fixture time required will be much shorter than for an assembly in which the bond area is limited and needs to bear a significant load in subsequent operations.

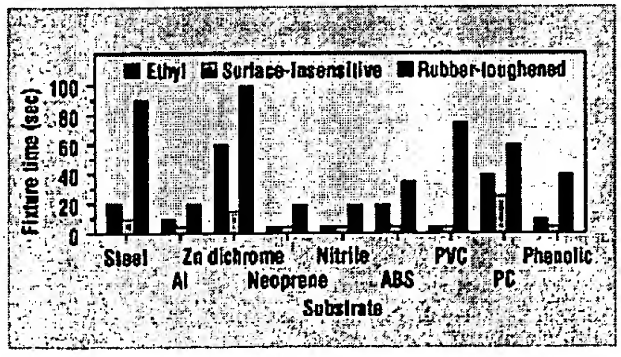


Figure 4. Fixture time for several types of cyanoacrylates. In these tests, the fixture time was defined as the time required to develop a shear strength of 14.5 psi by ASTM D 1002.

From the data in Figure 4, some interesting trends can be noted. As would be expected, the surface-insensitive cyanoacrylate generally fixtured fastest, followed closely by

the ethyl cyanoacrylate, while the rubber-toughened cyanoacrylate had the longest fixture times. The difference between the ethyl cyanoacrylate and the surface-insensitive cyanoacrylate was most significant on the acidic surface of zinc dichromated steel, where the surface-insensitive cyanoacrylate had a fixture time of 15 seconds compared with 60 seconds for the ethyl. The longer fixture time of the rubber-toughened product is characteristic of these products and represents one of the trade-offs associated with earlier-generation rubber-toughened cyanoacrylates. Time to complete cure generally follows the trends seen in fixture speeds, with most cyanoacrylates reaching full strength in 24 hours while the rubber-toughened products require a week to develop ultimate bond strength.

Since the cure of cyanoacrylates is initiated by the presence of surface moisture, it is not surprising that relative humidity can have a strong effect on cure speed. Generally, if the relative humidity falls below 30%, the cure rate will drop dramatically. It is best to use a surface-insensitive product in this situation or an accelerator if the humidity cannot be maintained at an acceptable level.

KEY PROPERTIES OF CURED (SOLID) CYANOACRYLATES

In its cured (solid) state, the cyanoacrylate properties of concern to end-users are those associated with performance of the adhesive in a bonded joint when subjected to different environmental and physical stresses. To help evaluate the suitability of various cyanoacrylates for device applications, the following properties are discussed in this section: initial and long-term shear strength, resistance to humidity and moisture, resistance to solvents, peel and impact strength, and the ability to withstand exposure to elevated temperatures.

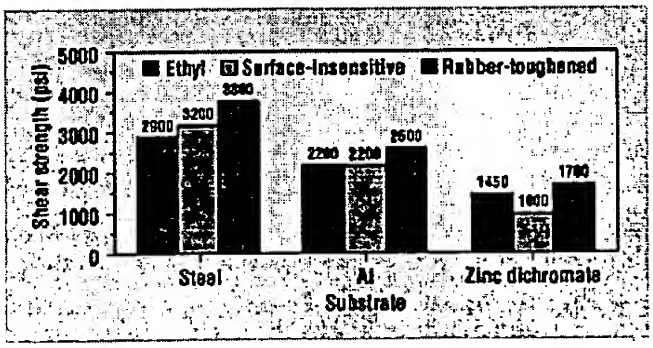


Figure 5. Typical bond strengths of several types of cyanoacrylates on common metals. Testing done according to ASTMD 1002.

Figure 6. Typical

bond strengths of several types of cyanoacrylates on common plastics. All samples tested according to ASTM D 4501

Initial Shear Strength. Once the cyanoacrylate adhesive has cured, one of the most important properties is the bond strength it has to various substrates. Figures 5 and 6 show typical shear strengths achieved with a variety of metallic and polymeric substrates. The rubber-toughened cyanoacrylates generally show the best bond strength to metallic substrates, whereas the ethyl and surface-insensitive cyanoacrylates demonstrate better performance on polymeric substrates. It should be noted that the difference in performance on metallic substrates between the various types of cyanoacrylates is not as distinct as the difference on polymeric substrates. On plastics, rubber-toughened cy-anoacrylates generally tend to have bond strengths that are from 25 to 50% of those achieved by surface-insensitive and ethyl cyanoacrylates.[2]

One substrate that poses a unique challenge for cyanoacrylates is glass. While the initial bond strength will often be high enough to break the glass, it drops dramatically after a number of weeks, resulting in a bond of negligible strength. This phenomenon demonstrates in a drastic way the importance of considering long-term bond strength when evaluating an adhesive for an application.

Long-Term Shear Strength. Once cured, cyanoacrylates form thermoplastic polycyanoacrylate, which is a stable, inert material at room temperature. Assemblies bonded with cyanoacrylate have shown acceptable long-term performance in a variety of applications. Typically, accelerated testing is done at high temperatures and extreme conditions to predict whether long-term bond performance will be acceptable. While these techniques are valuable, it is desirable to see actual long-term data in order to substantiate predicted values.

An investigation of the durability of the long-term bond strength of cyanoacrylates on electroless-nickel-plated steel was performed to address this need. This material was selected as the test substrate because its smooth surface and lack of reactivity make it particularly difficult to bond; consequently, it would represent a worst-case scenario for maintaining long-term bond strength. The results of this evaluation are shown in Figure 7. As can be seen, after 3

years the bond strength has yet to show any significant change.

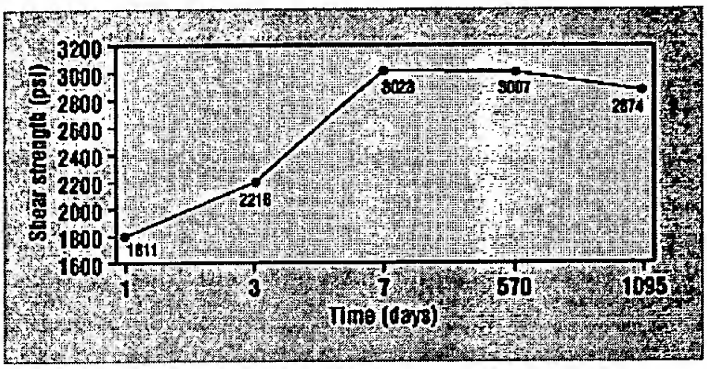


Figure 7. Long-term bond durability of rubber-toughened cyanoacrylate on electroless nickel. Testing done according to ASTM D 1002.

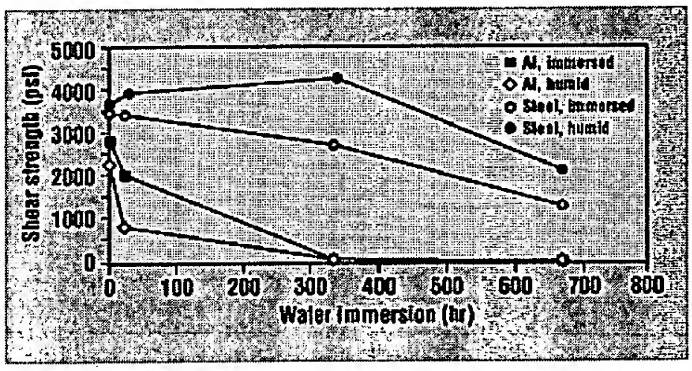


Figure 8. Effect of water immersion on bond strength of rubber-toughened cyanoacrylate to steel and aluminum. Testing done according to ASTM D 4501. Bond area 0.5 x 1.0 in., no induced gap. Humid = 120°F, condensing humidity.

Humidity and Moisture Resistance. Because cyanoacrylates are extremely polar, a reasonable concern is that a polar solvent such as water could detrimentally affect their long-term bond strength. Testing has shown that the resistance of a cyanoacrylate-bonded joint to long-term exposure to humidity or immersion in water is dramatically affected by the type of substrate. For example, on metallic substrates such as aluminum and steel, exposure to humidity leads to a drop-off in bond strength for all types of cyanoacrylates. Figure 8 shows the effect of humidity and immersion in water for rubber-toughened cyanoacrylates on aluminum and steel. Data for rubber-toughened cyanoacrylates is shown because they typically demonstrate

the best performance in water or humid environments. Consequently, using these products with no induced gap should represent the best-case scenario for a cyanoacrylate bond. Even under these conditions, the trends are clear. On steel, there was a decline in bond strength over time; on aluminum, the strength dropped off more abruptly, after just 2 weeks of immersion. On polymeric substrates such as ABS and polycarbonate, however, even standard ethyl cyanoacrylates showed good bond-strength retention after 4 weeks of immersion in water (Figure 9). Similar results have also been seen with neoprene rubber.

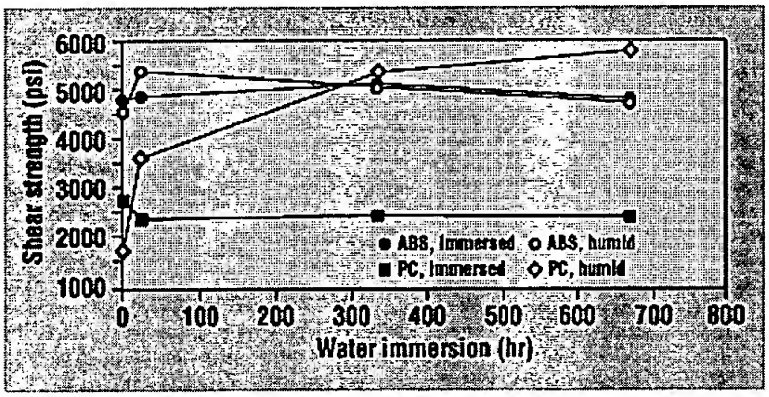


Figure 9. Effect of water immersion on bond strength of ethyl cyanoacrylate to ABS and polycarbonate. Testing dome according to ASTM D 4501. Bond area 0.5 x 1.0 in., no induced gap. Humid = 120°F, condensing humidity.

The ability of cyanoacrylates to resist attack from moisture when bonded to polymeric substrates can be most drastically tested by subjecting bonded assemblies to autoclaving. The autoclaving process combines the environmental stresses of high temperature, high-pressure, and humidity. As such, it provides a good indicator of the ability of adhesives to withstand exposure to moisture.

As part of an evaluation of the effect of repeated sterilization cycles on adhesives, cyanoacrylate-bonded assemblies were subjected to multiple autoclaving cycles. Each cycle involved a pre-evacuation of air from the chamber, followed by immersion in pure steam at 270°F for 6 minutes. After 100 autoclaving cycles, polycarbonate assemblies bonded with surface-insensitive cyanoacrylates and toughened cyanoacrylates consistently experienced substrate failure when tested for bond strength. When bonded to polyetherimide, however, 10 cycles of autoclaving reduced bond strength of both types of cyanoacrylate by 50%; after

100 cycles, bond strength had decreased to approximately 25% of the initial bond strength. These data show that while cyanoacrylates have demonstrated excellent bond-strength retention on several thermoplastics in humid environments, testing should be done before extrapolating such results to other polymeric substrates.

Environment	Temperature (°F)	% Initial Bond Strength Retained After:		
		100 Hours	500 Hours	1000 Hours
Leaded gas	72	100	100	100
Motor oil (10W30)	104	100	100	95
Ethanol	72	100	100	100
Isopropanol	72	100	100	100
Freon T.A.	72	100	100	100

Table I. Typical solvent resistance of ethyl cyanoacrylates. All testing done on bonded steel lap shears.

Environment	Temperature (°F)	% Initial Bond Strength Retained After:		
		100 Hours	500 Hours	1000 Hours
Leaded gas	72	90	70	70
Motor oil (10W30)	104	85	85	85
Ethanol	72	95	95	80
Isopropanol	72	75	75	75
Freon T.A.	72	90	90	80

Table II. Typical solvent resistance of rubber-toughened cyanoacrylates. All testing done on bonded steel lap shears.

Solvent Resistance. Even though cyanoacrylates are

thermoplastics, they generally have very good resistance to many commonly used solvents. Tables I and II show resistance data for ethyl and rubber-toughened cyanoacrylates; the chemical resistance of surface-insensitive cyanoacrylates is generally be similar to that of ethyl cyanoacrylates. It is always best to minimize the gap in any adhesive joint that will be subject to chemical exposure. This minimizes the surface area of the adhesive that can be attacked by the chemical and makes it more difficult for the chemical species to diffuse into the bond joint. The solvent resistance of rubber-toughened cyanoacrylates is slightly lower than that of untoughened cyanoacrylates. This may be because the rubber in the cyanoacrylate matrix has a lower solvent resistance than the polycyanoacrylate, thus leading to lower overall resistance for the entire system. Because more-polar solvents such as nitromethane and acetone will rapidly dissolve cyanoacrylate adhesive, caution should be used in bonding assemblies with cyanoacrylates if exposure to these solvents is likely.

Peel and Impact Strength. While cyanoacrylate adhesives are known for achieving outstanding shear strength on a wide variety of substrates, they generally tend to have poor peel and impact strength because they are extremely brittle. To address this limitation, several different approaches have been employed. Initial attempts at improving the peel strength of cyanoacrylates involved the use of anhydrides and other toughening additives. It was thought that these species helped disturb the crystallinity of the polycyanoacrylate and thus produced a more ductile polymer. These approaches did enhance peel strength compared with that of standard cyanoacrylates; however, further improvements were needed to give cyanoacrylates the peel strength required for many applications.

Cyanoacrylate Type	Peel Strength (lb/in. of width)
Standard ethyl cyanoacrylate	<3
Maleic anhydride—toughened cyanoacrylate	10
Rubber-toughened	40

cyanoacrylate	

Table III. Comparison of peel strength values for several types of cyanoacrylates tested according to ASTM D1876 on degreased steel.

An obvious path to improving the peel strength of cyanoacrylates involved compounding rubber into the adhesive. Ideally, the rubbery phase would absorb impact energy and prevent cracks from propagating through the adhesive matrix. Unfortunately, the tendency of cyanoacrylates to rapidly polymerize made it difficult to successfully blend them with rubber and produce a stable product. Consequently, it took years of research to find appropriate rubbers and compounding techniques that allowed rubber-toughened cyanoacrylates to be created. The resulting products featured peel strengths that enabled them to be used in applications that previous generations of cyanoacrylates had been too brittle to endure. Table III compares the peel strengths obtained with standard, maleic anhydride–toughened, and rubber-toughened cyanoacrylates. As mentioned previously, the improved peel and impact strengths of the rubber-toughened cyanoacrylates are offset by longer fixture times, lower bond strengths to polymeric substrates, and a slightly lower solvent resistance compared with ethyl and surface-insensitive cyanoacrylates.

Thermal Resistance. Once they cure, standard ethyl cyanoacrylates form a thermoplastic resin with a glass-transition temperature (T_g) of approximately 260°–266°F. Upon heating to 180°–220°F, cyanoacrylates soften considerably and consequently drop dramatically in the load that they are able to bear in a bonded assembly. Upon heating to 320°F, they begin to depolymerize and revert to cyanoacrylate monomer. Under certain conditions, slow depolymerization of the polymerized cyanoacrylate has been noted even at lower temperatures—in the 180°–250°F range.[3] As a result of these considerations, standard cyanoacrylates have not been widely used in high-temperature applications.

To address these limitations, cyanoacrylate manufacturers have taken two approaches. The first was the development of cyanoacrylates based on the allyl cyanoacrylate monomer (Figure 1). This monomer yields a cured polymer that can be

cross-linked through the allyl group and thus offer improved strength retention at higher temperatures. The allyl cyanoacrylate initially forms a thermoplastic resin through anionic polymerization. Because of the structure of the allyl monomer, this thermoplastic has a T_g of only 230°F. Since the temperatures required to thermoset the allyl cyanoacrylate are much higher than the glass-transition temperature of the thermoplastic resin that initially forms, the adhesive cannot bear a load during the heat-cure step. As a result, parts must be fixtured in some fashion during heat cure. Unfortunately, the cross-linking reaction through the allyl group is very slow, even at temperatures as high as 350° F. For example, after 100 hours at 350°F, a hot strength of only 389 psi was achieved.[3] Due to these processing limitations, allyl cyanoacrylates have not adequately met the needs of end-users with thermally demanding applications.

The other approach used to produce a cyanoacrylate with improved thermal stability was the modification of rubber-toughened cyanoacrylates through proprietary additives. Rubber-toughened cyanoacrylates were considered to be the best candidates for developing thermally resistant cyanoacrylates for the following reason. It is believed that after room-temperature cure, most cyanoacrylates have a certain level of residual uncured monomer that acts as a plasticizer. When heated, the increased mobility of the monomer in the polymer matrix leads to complete cure of the monomer. As this unreacted monomer cures, it induces stresses in the bond line via two mechanisms. First, the reduction in the amount of unreacted monomer from the polymer matrix results in a loss of the plasticizing effect. Secondly, shrinkage occurs as the monomer cures, which introduces additional stresses to the bond line. This phenomenon is considered to be the reason that standard cyanoacrylates show a loss of bond strength after exposure to elevated temperatures, particularly when used to bond rigid substrates. It is thought that the rubber in the rubber-toughened cyanoacrylates allows them to more easily absorb these stresses without loss of integrity at the adhesive/substrate interface.[4]

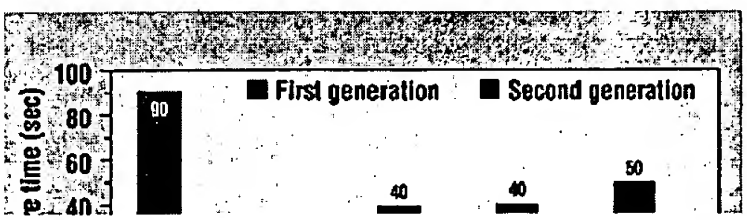


Figure 10. Fixture time for first- and second-generation thermally resistant cyanoacrylates. In these tests, fixture time was defined as the time required to develop a shear strength of 14.5 psi by ASTM D 1002.

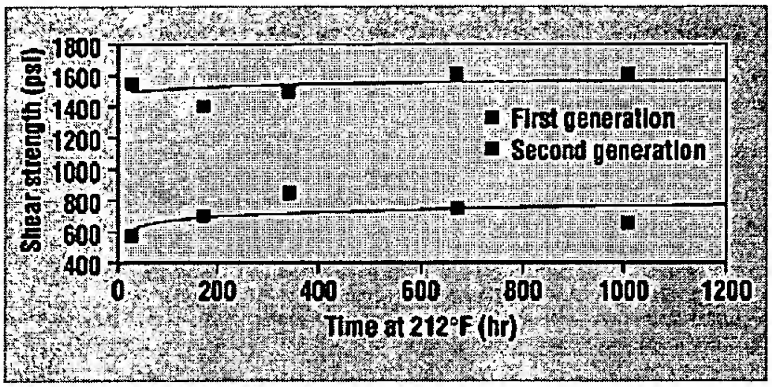


Figure 11. Hot-strength heat-aging of first- and second-generation thermally resistant cyanoacrylates on polycarbonate. All testing done on PC block shears in accordance with ASTM D 4501. All samples tested at 212°F.

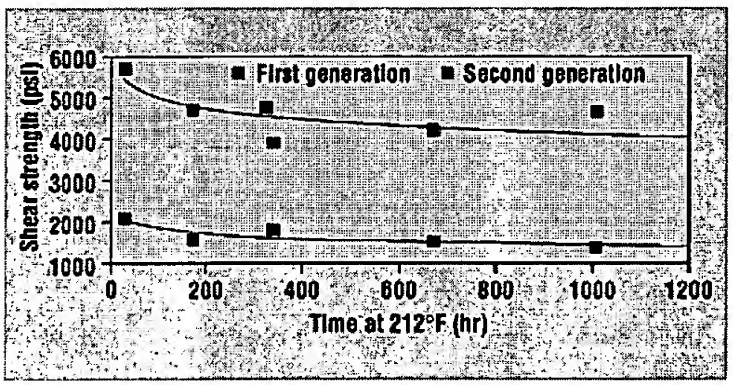


Figure 12. Heat-aging of first- and second-generation thermally resistant cyanoacrylates on polycarbonate. All testing done on PC block shears in accordance with ASTM D 4501. All samples tested at room temperature.

The application of proprietary additive technology to rubber-toughened cyanoacrylates has resulted in a class of thermally resistant, rubber-toughened cyanoacrylates that offer good hot strength and long-term bond-strength retention up to 250°F. On steel lap shears, this class of adhesives has maintained bond strengths in excess of 1000 psi at 250°F after being heat-aged for 1000 hours at 250°F. Since these products require no secondary heat-cure step, they avoid many of the processing difficulties of the allyl-based

cyanoacrylates; because they are based on rubber-toughened formulations, they have the same high peel strength. However, they also have the long fixture times and the lower bond strengths to polymeric substrates that characterize rubber-toughened cyanoacrylates.

NEW DEVELOPMENTS IN CYANOACRYLATE TECHNOLOGY

The introduction of thermally resistant, rubber-toughened cyanoacrylates substantially improved the performance properties available in a cyanoacrylate adhesive. These improvements have been further enhanced with the introduction of a second generation of thermally resistant, rubber-toughened cyanoacrylate adhesives that also offer fast fixture times and improved bond-strength performance on polymeric substrates. Figure 10 shows a comparison of typical fixture times for the first generation of thermally resistant, rubber-toughened cyanoacrylates and the newest type of products. Figures 11 and 12 present a comparison of bond strength to polycarbonate for first- and second-generation thermally resistant, rubber-toughened cyanoacrylates. The improvement in bond strength to polymeric substrates offered by the second-generation products is particularly notable after heat-aging. These newer adhesives also maintain the good high-temperature bond-strength retention to metallic substrates of the first-generation products, as shown in Figures 13 and 14.

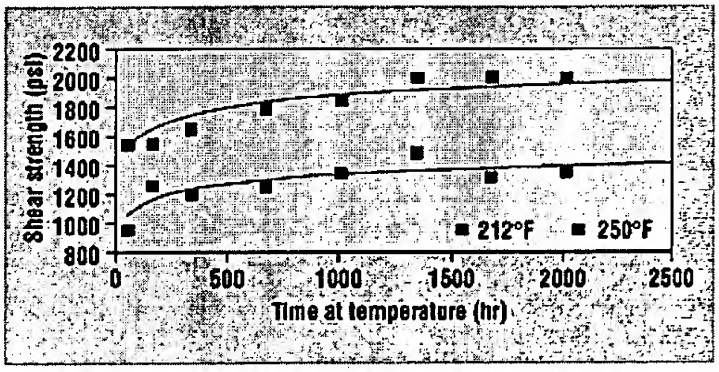


Figure 13. Hot-strength heat-aging of second-generation thermally resistant, rubber-toughened cyanoacrylates on steel lap shears. All testing done in accordance with ASTM D 1002. Assemblies tested at temperature indicated.

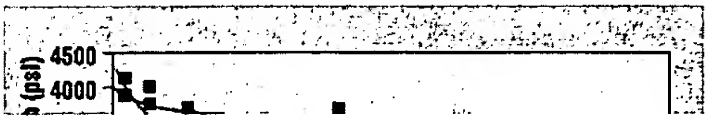


Figure 14. Heat-aging of second-generation thermally resistant, rubber-toughened cyanoacrylates on steel lap shears. All testing done in accordance with ASTM D 1002. Samples tested at room temperature.

CONCLUSION

Cyanoacrylate adhesives provide unique benefits that make them well suited for use in medical device manufacturing processes. Advances in cyanoacrylate technology have led to the development of a wide variety of adhesives offering performance and process improvements for device manufacturers. Some of these products include surface-insensitive cyanoacrylates, which cure well on acidic surfaces; low-odor, low-bloom cyanoacrylates, which offer a less-irritating odor; rubber-toughened cyanoacrylates, which feature improved peel strength and impact resistance; and thermally resistant cyanoacrylates, which provide long-term performance at temperatures as high as 250°F. The latest generation of thermally resistant cyanoacrylates combines the benefits of rubber toughening with thermal resistance and surface insensitivity, resulting in a product with the ease of use of a one-part formulation and the performance of a structural adhesive.

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Wound Adhesives, 2-Octyl Cyanoacrylate

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Synonyms and related keywords: tissue glues, octyl-2 cyanoacrylate, butyl-2-cyanoacrylate, Dermabond

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The cyanoacrylates first were synthesized in 1949 by Airdis. Coover et al described their adhesive properties and suggested their possible use for surgical adhesives. In the early 1960s, various surgical applications were investigated for these adhesives.

Cyanoacrylates can be synthesized by reacting formaldehyde with alkyl cyanoacetate to obtain a prepolymer that, by heating, is depolymerized into a liquid monomer. The monomer then can be modified by altering the alkoxycarbonyl (-COOR) group of the molecule to obtain compounds of different chain lengths. Upon application to living tissues (water or base), the monomer undergoes an exothermic hydroxylation reaction that results in polymerization of the adhesive. The shorter-chain derivatives tend to have a higher degree of tissue toxicity than the longer-chain derivatives.

Inflammation, tissue necrosis, granulation formation, and wound breakdown can occur when cyanoacrylates are implanted subcutaneously. The process causing the histologic toxicity is thought to be related to the by-products of degradation, cyanoacetate and formaldehyde. The local concentrations of these breakdown products are proportional to the rate of degradation (an

aqueous degradation process) of the parent compound. Therefore, slower degradation rates result in less toxicity to the tissues. This is explained by the hypothetical possibility that slowly degrading compounds release degradation products more gradually, thereby permitting more effective clearance and invoking a less intense inflammatory response. The longer-chain compounds degrade much more slowly than the shorter-chain compounds, hence the lower reactivity of the longer-chain compounds.

Until recently, butyl-2-cyanoacrylate was the only commercially available cyanoacrylate tissue adhesive. Although butyl-2-cyanoacrylate is effective in closing superficial lacerations under low tension, it has several limitations. Several studies have shown wound-breaking strength in wounds repaired with butyl-2-cyanoacrylate to be equal to that in wounds repaired with sutures at 5-7 days; however, on day 1, breaking strength with the tissue adhesive is only approximately 10-15% of that in a wound sutured with 5-0 monofilament. After polymerizing, the adhesive becomes brittle and is subject to fracturing when used in skin creases or long incisions. This restricts the use of adhesives to areas of low tension, thus limiting their use for incision repair. Butyl-2-cyanoacrylate has been used widely with good cosmetic outcomes for various plastic surgical procedures (eg, upper lid blepharoplasty, facial skin closure, scalp wound closure).

The polymer 2-octyl cyanoacrylate was formulated to correct some of the deficiencies of the shorter-chain cyanoacrylate derivatives. As an 8-carbon alkyl derivative, this polymer should be less reactive than the shorter-chain derivatives. The slower degradation of the octyl derivatives may result in lower concentrations of the cyanoacrylate polymer by-products in surrounding tissues, resulting in less inflammation. Additionally, plasticizers are added to produce a more pliable and tissue-compatible product that flexes with the skin and remains inherent for longer periods of time. The 3-dimensional breaking strength of 2-octyl cyanoacrylate is 3 times that of butyl-2-cyanoacrylate and is closer to that of a 5-0 monofilament suture. This stronger flexible bond may allow its use on longer incisions.

The Food and Drug Administration (FDA) has approved 2-octyl cyanoacrylate for closure of incised skin. In addition to its surgical adhesive indication, 2-octyl cyanoacrylate (Dermabond) was approved by the FDA in January 2001 for use as a barrier against common bacterial microbes including certain staphylococci, pseudomonads, and *Escherichia coli*.

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Cost analysis has found that the use of tissue adhesives can significantly decrease health care costs and is preferred by patients. Adhesives also provide a needle-free method of wound closure, an important consideration because of blood-borne viruses (eg, HIV). The cyanoacrylates function as waterproof occlusive dressings, have antimicrobial properties against gram-positive organisms, and may decrease infections. They have been demonstrated to decrease histologic and clinical infection rates in contaminated wounds when compared to closure with sutures. If the adhesives are used improperly and are implanted into the wound, they can cause a foreign-body reaction and actually may increase infection rates.

The following discussion is limited to 2-octyl cyanoacrylate. Moreover, this text is designed to be only a guideline; as always, physicians should use their own discretion in the use of these materials. Although tissue adhesives have many advantages, their successful incorporation into the physician's practice depends on understanding the indications, contraindications, and proper

method of application. Without understanding these concepts, results are more likely to be unsatisfactory and advantages of adhesives are more likely to be lost.

The adhesive can be used topically to close skin incisions and lacerations alone, or it can be used in conjunction with deep sutures. Generally, the octyl products can be used in place of nonabsorbable sutures for primary closure of skin incisions and lacerations on the face. For facial incisions and lacerations that are under tension and when closing incisions and lacerations on the extremities and torso, deep (subcutaneous) sutures are recommended.

The adhesive should not be used on the oral mucosa, hands, feet, or joints, where repetitive movement and washing may cause the adhesives to slough prematurely. Other types of wounds that are not optimal for cyanoacrylates are decubitus ulcers, stellate lacerations, animal or human bites, and nonsurgical puncture wounds. The adhesive does not replace the requirement for good quality wound care. Wounds still need careful examination and exploration with irrigation and debridement when appropriate. These types of wound preparations still may require local anesthetic.

In learning to apply tissue adhesives, the most important concept is that they are for topical closure only. Give special care to ensure the adhesive will not leak between the wound edges. If used properly, the adhesive acts as a strong bridge to hold the well-opposed wound edges together. If placed in the wound, it acts as a barrier to proper epithelialization and may slow healing. Once in the wound, the adhesive also has the potential to cause a foreign-body reaction and to increase the incidence of infection.

Toriumi et al have published an excellent paper on the use of 2-octyl cyanoacrylate. They underscore two other important principles, which are the need to reduce skin tension at the site of the laceration and the need to ensure no dead space is present before sealing with the tissue adhesive.

Deep dermal sutures (vertical mattress stitches) are used to bring the skin edges into everted apposition. The everted edges are extremely important to successful closure with tissue adhesives, since they prevent scar broadening and improve the cosmetic result. The everted skin apposition should be maintained with forceps or fingers during the application of the 2-octyl cyanoacrylate. For best results, a thin layer should be applied over the epidermis and allowed to dry for approximately 20-30 seconds. This method prevents pooling and running of the tissue adhesive, and it also provides a layer of protection from the heat generated by the exothermic polymerization. Subsequent layers of cyanoacrylate then are applied over the top of this initial layer.

Several clinical studies have shown that 2-octyl cyanoacrylate provides cosmetic results equal to those of sutures. Therefore, given the speed and efficacy of this new tissue adhesive, it should firmly establish itself in the treatment repertoire for closure of the skin. Future investigations with this product no doubt will expand its use.

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